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Topiramate in Trigeminal Neuralgia: A Randomized, Placebo-controlled Multiple Crossover Pilot Study

*Ian Gilron, †Susan L. Booher, †Janet S. Rowan, and *Mitchell B. Max

**Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, and †Department of Nursing, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA*

Summary: We conducted a pilot study to evaluate the efficacy of topiramate in trigeminal neuralgia using a randomized, double-blind, placebo-controlled, two-period crossover design. Three patients were enrolled in and completed the study. All three patients responded to topiramate in this main study and entered a subsequent confirmatory study consisting of three topiramate-placebo crossovers. In the main study, topiramate reduced pain by 31%, 42%, and 64% in the three patients ($p = 0.04$). However, topiramate showed no effect in the confirmatory study. Given that trials of less common pain conditions are fraught with low patient recruitment rates, a multiple crossover design provides more information, which is important in conditions associated with considerable pain fluctuation. Larger trials are needed to more precisely estimate the effect of topiramate in trigeminal neuralgia. **Key Words:** Topiramate—Trigeminal neuralgia—Facial neuralgia—Pain—Placebo—Crossover studies

Because current drug treatment of idiopathic trigeminal neuralgia eventually fails in up to 56% of patients, additional treatments are needed (1,2). We became interested in studying the new anticonvulsant topiramate after two studies in our clinic showed that the AMPA/kainate glutamate receptor antagonist LY293558 reduced pain evoked by light touch in volunteers treated with intradermal Capsaicin (3) and pain evoked by facial movement after oral surgery (4). In patients with trigeminal neuralgia, pain is often evoked by either light touch or movement. The receptor antagonist LY293558 is available only for brief intravenous infusion, but the orally available topiramate has been reported to block kainate-specific glutamate currents (5). Topiramate has other pharmacologic actions that might reduce pain, including state-dependent sodium channel blockade (6) and potentiation of gamma-aminobutyric acid–induced chloride flux (7). To date, clinical reports in neuropathic pain have been limited to a single case report of a patient with intercostal neuralgia (8) and an open-label study of patients with mixed neuropathies (9). Therefore, we studied the analgesic effects of topiramate in several patients with trigeminal neuralgia, using a randomized, double-blind, placebo-controlled, multiple crossover design.

Address correspondence and reprint requests to Mitchell B. Max, National Institutes of Health, Room 3C-405, Bethesda, MD 20892–1258, USA.

METHODS

Patients

This study was approved by the Institutional Review Board of the National Institute of Dental and Craniofacial Research. Patients with idiopathic trigeminal neuralgia (which may include recurrent trigeminal neuralgia following invasive peripheral nerve or intracranial procedures) were recruited for this study. Screening of eligible patients included a general physical examination and laboratory tests. Patients with multiple sclerosis or with continuous pain and dense sensory loss related to an invasive procedure (*i.e.,* anesthesia dolorosa) were excluded.

Treatment

Topiramate was compared with an inert placebo in a randomized, double-blind, two-period crossover study ("main study"). After maintaining a stable dose of other pain medications for 2 weeks, patients entered a

1-week baseline period, followed by two 12-week drug treatment periods separated and concluded by 2-week washout periods. The treatments, given in random order, were as follows: topiramate beginning at 25 mg daily and titrated to a maximum daily dosage of 800 mg or inert placebo.

A study nurse telephoned the patients twice weekly to titrate medication dosage and to assess pain, side effects, and study compliance. During the first 8 weeks of each period (titration phase) the medication was increased by 25–50 mg/d (topiramate) or by a corresponding number of matching capsules (placebo) at every telephone contact unless the patient reported complete pain relief, side effects interfering with daily activities, or that the maximum daily study drug doses were reached. During weeks 9–12 (maintenance phase) the maximal tolerated dose was maintained at a constant level.

Outcome Evaluation

Patients rated pain once daily at bedtime. The primary outcome measure was overall daily pain rated with a 0–10 numerical scale ("Taking into account all the different types of pain you experience, rate your overall facial pain for the past 24 hours. Zero indicates no pain and 10 indicates the most pain imaginable for 1 day"). Secondary measures included the intensity, frequency, and duration of paroxysmal pains. The intensity of the worst pain paroxysm experienced over the previous 24-hour period was rated by choosing a number from a 0–20 numerical grid upon which 13 verbal pain intensity descriptors were interpolated (10). Frequency was rated by counting the number of paroxysms experienced that day. Also, patients estimated the average duration of all paroxysms for that day. Patients were asked about side effects by the study nurse using the open-ended question: "Have you experienced any side effects since the last phone call?"

Confirmatory Drug-Placebo Comparisons

Patients with a pain score favoring topiramate over placebo by at least one unit on the 0–10 overall pain measure during the main study were offered the opportunity to enter a confirmatory study (11). This confirmatory comparison consisted of three 8-week segments. Within each segment, the patient took 4 consecutive weeks of topiramate and 4 weeks of placebo (assigned in random order) under double-blind conditions. The topiramate dose was the maximal tolerated dose that wads determined during participation in the main study. Evaluation procedures were the same.

Data Analysis

Pain ratings during placebo and topiramate treatment were compared using paired Student *t* tests for each patient individually through all treatment periods, and for the three patients considered together in the main and confirmatory studies.

RESULTS

Main Study

Three patients with trigeminal neuralgia were enrolled and all three completed the study. The clinical characteristics of these patients are summarized in Table 1. In the last 2 weeks of the 12-week treatment period there was less pain while receiving topiramate than while receiving the placebo (Table 2 and Fig. 1). As measured by the 0–10 overall daily pain scale, pain during topiramate treatment in the main study compared with placebo was decreased by 31%, 42%, and 64% in the three patients ($p = 0.04$). Paroxysm frequency was decreased by 10% to 93%, paroxysm intensity was decreased by 3% to 32%, and paroxysm duration was decreased by 77% in one patient but increased by 88% to 290% in the two other patients; however, none of these changes was significant. Adverse effects of at least moderate severity during treatment with topiramate, but not placebo, included irritability and diarrhea (in two patients) and fatigue/sedation, hyperactivity, nausea, abdominal cramps, lightheadedness, and cognitive impairment (in one patient each).

TABLE 1. *Patient characteristics, concurrent medications, treatment sequences and topiramate doses*

Patient	Age	Sex	Duration of pain (y)	Pain location	Sensory examination	Previous procedures	Medications continued during study	Treatment sequence	Top MTD (mg/d)
1	66	M	30	R-V2, R-V3	↓PP + ↓LT (R-V3)	GA; MVD	CBZ, Bac	plac→top	250
2	53	F	32	R-V2, R-V3 T(R-V1, V2, V3);	↓PP (R-V1, V	GA × 3	Clon, TCA	top→plac	600
3	40	F	5	L-V2, L-V3	Normal	–	CBZ, GBP	plac→top	75

R, right; L, left; V1, opthalmic division; V2, maxillary division; V3, mandibular division; PP, pin prick; LT, light touch; GA, gasserian ganglion ablation; MVD, microvascular decompression; Top, topiramate; Plac, placebo; CBZ, carbamazepine; Bac, baclofen; Clon, clonazepam; TCA, tricyclic antidepressants; GBP, gabapentin; MTD, maximum tolerated dose.

TABLE 2. *Outcome measures* during main and confirmatory studies*

	Main study			Crossover #1			Crossover #2			Crossover #3		
Patient	Plac	Top	% reduction	Plac	Top	% reduction	Plac	Top	% reduction	Plac	Top	% reduction
						Overall Daily Pain on 0–10 Scale						
1	2.8	1.0	64.3	2.0	1.5	25.0	2.0	1.9	5.0	2.0	2.0	0.0
2	6.6	4.5	31.8	5.0	4.9	2.0	–	–	–	–	–	–
3	2.8	1.6	42.9	2.6	2.9	−11.5	2.4	1.4	41.7	1.8	3.4	−88.9
						Paroxysm Frequency (#/d)						
1	31.4	28.2	10.2	35.0	34.6	1.1	35.0	27.1	22.6	31.4	23.0	26.8
2	89.6	33.1	63.0	84.9	77.1	9.2	–	–	–	–	–	–
3	63.9	4.3	93.3	62.1	36.4	41.4	33.9	25.0	26.3	51.4	81.1	−57.8
						Paroxysm Intensity on 0–20 scale						
1	12.8	12.4	2.5	12.9	11.4	11.6	12.1	11.4	5.8	13.3	10.6	20.3
2	18.3	12.5	31.6	16.0	15.8	1.3	–	–	–	–	–	–
3	17.4	16.5	4.9	17.6	17.6	0.0	15.8	14.9	5.7	14.6	16.0	−9.6
						Paroxysm Duration (sec)						
1	4.0	7.5	−87.5	4.0	4.9	−22.5	4.0	4.0	0.0	2.0	2.0	0.0
2	71.6	16.8	76.6	31.6	33.4	−5.7	–	–	–	–	–	–
3	2.9	11.4	−290.2	2.2	2.0	9.1	1.0	1.1	−10.0	1.0	1.0	0.0

Plac, placebo; top, topiramate.
* Presented data are means from the last 2 weeks of each treatment period.

Confirmatory Study

All three patients entered the confirmatory study, but only patients 1 and 3 completed all three crossover pairs (Table 2). For each patient, we calculated a single mean of daily pain ratings for the last 2 weeks for each treatment of each completed crossover period. Considering each patient individually through all completed treatment periods of the confirmatory study, no significant pain reduction by topiramate was observed (Table

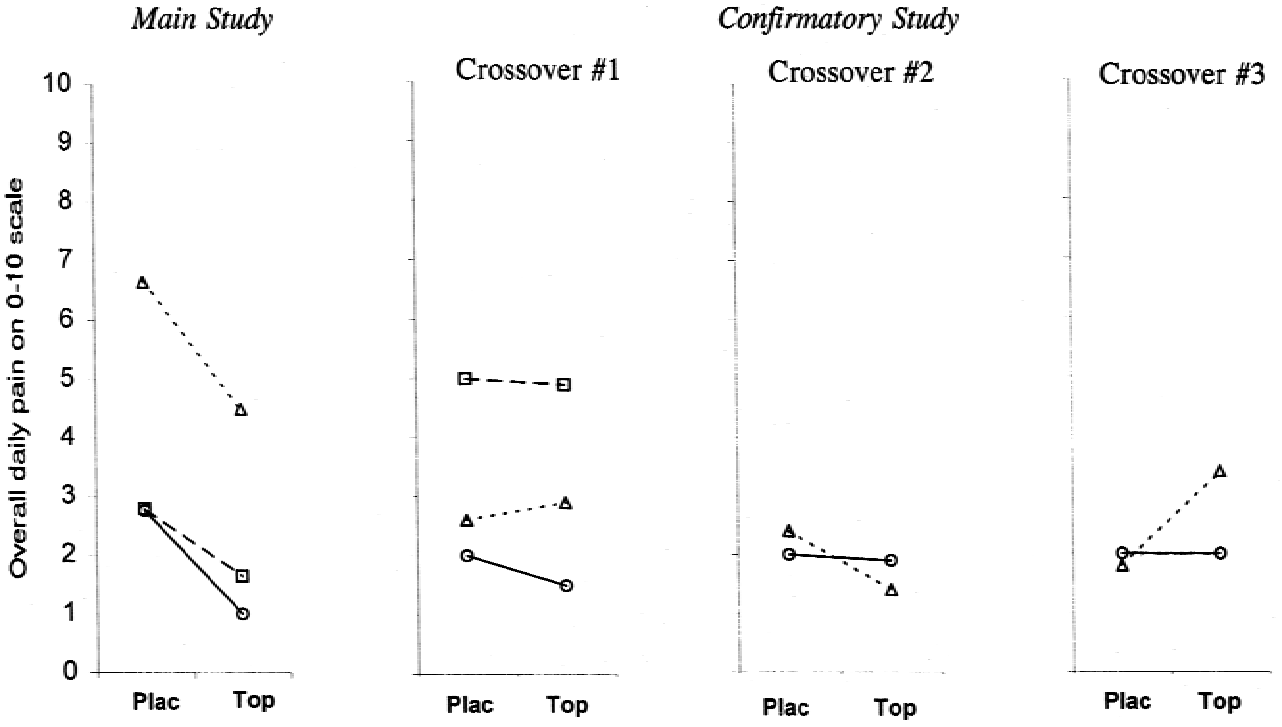

FIG. 1. Overall daily pain for each patient during treatment with placebo is connected to their respective scores during treatment with topiramate. For each patient, presented data are means from the last 2 weeks of each treatment period. Although treatment order within each pair was randomly assigned, individual results are presented in a uniform order for clarity. In the main study only, topiramate reduced pain by 31%, 42%, and 64% in the three patients ($p = 0.04$). Considering data from both the main and confirmatory studies, there were no significant pain reductions using paired Student *t* tests for each patient individually through all treatment periods or for the three patients considered together in the main and confirmatory study. Plac, placebo; Top, topiramate.

2 and Fig. 1). Also, considering the three patients together through all completed treatment periods of the confirmatory study, no significant pain reduction by topiramate was observed.

Considering each patient individually through all completed treatment periods of both the main and confirmatory studies, no significant pain reduction by topiramate was observed. Considering the three patients together through all completed treatment periods of both the main and confirmatory studies, no significant pain reduction by topiramate was observed.

DISCUSSION

This study provides controlled clinical data on the effects of topiramate in the treatment of trigeminal neuralgia. Topiramate was well tolerated as an add-on to other antineuralgic drugs. Patients 1 and 2 historically observed no change in the pattern of their pain following the gasserian ganglion ablative procedures they underwent. However, it should be noted that these patients demonstrated sensory abnormalities in the trigeminal nerve distribution and that mechanisms of pain in these patients may differ from those in patients with neurosurgically untreated trigeminal neuralgia.

In the main study, pain was reduced by 31% to 64%. Despite an initial positive response in all three patients, no significant analgesic effect was observed in the confirmatory study; possible explanations could include chance variation or pharmacologic tolerance. However, we cannot rule out the possibility of an initial placebo effect in the main study, elicited by the side effects patients observed with topiramate, which diminished over time. Without the subsequent confirmatory study, data from the main study alone would have suggested a strong analgesic effect of topiramate. Considering data from both the main and confirmatory studies allows for a more cautious interpretation than consideration of data from the main study alone. Given that trials of less common pain conditions are fraught with low patient recruitment rates, the use of a multiple crossover design may provide more rigorous clinical data. This guards against the reporting bias that may influence the usual uncontrolled case report and is particularly important in conditions where pain intensity fluctuates widely. Larger trials are needed to more precisely estimate the effect of topiramate in trigeminal neuralgia.

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